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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Francis J. GILES et al.	:	Examiner: Cybille Delacroix-Muirheid
Serial No.: 10/729,387	:	Group Art Unit: 1614
Filed: December 8, 2003	:	

For: PHARMACEUTICAL COMBINATIONS AND METHODS FOR THE TREATMENT OF LEUKEMIA

SUBMISSION OF DECLARATIONS UNDER RULE 132

MAIL STOP – AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In the Reply filed October 19, 2005, Applicants indicted that they were filing therewith copies of Rule 132 Declarations by each of the two inventors. However, upon review of applicants file and the PAIR system, it does not appear that copies of the Declarations were attached to the October 19, 2005 Reply.

In any event, attached hereto are copies of the Declarations under Rule 132 executed by each of the two inventors. These Declarations confirm that, to the extent the claimed invention is disclosed in these publications, such disclosures are of the invention of Francis Giles and Srdan Verstovsek, the two co-inventors of the present application. Therefore, this abstract does not constitute prior art with respect to the claimed invention. See, e.g., In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Filed: November 9, 2005

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Francis J. GILES et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/729,387 : Group Art Unit: 1614

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For: PHARMACEUTICAL COMBINATIONS AND METHODS FOR THE TREATMENT OF LEUKEMIA

DECLARATION BY SRDAN VERSTOVSEK UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

I, Srdan Vestovsek, being duly warned, declare that:

I and Francis J. Giles are the co-inventors of the claimed invention in the above-captioned application (see the attached list of claims).

I have been an employee of University of Texas, M. D. Anderson Cancer Center since 1998.

By virtue of an agreement between between University of Texas, M. D. Anderson Cancer Center and Shire Biochem Inc., the instant application is assigned to Shire Biochem Inc.

By virtue of an agreement between The University of Texas, M. D. Anderson Cancer Center and Shire Biochem Inc., Shire Biochem retained the services of The University of Texas, M. D. Anderson Cancer Center to perform, in the ordinary course of business, preclinical laboratory study entitled "Preclinical evaluation of Troxacitabine and STI571 combination treatments of Philadelphia chromosome-positive STI571-resistant leukemia." The study was performed for Shire Biochem, and particularly under the direction, supervision and control of myself and Francis J. Giles. The results of this study are presented in the following coauthored by myself, Francis J. Giles, and also Nada Orsolic, Miloslav Beran, Jorge Cortes, Maher Albitar, and Hagop Kantarjian:

"Troxatyl and STI571 Combination Therapy for Chronic Myeloid Leukemia: Preclinical In Vitro and In Vivo Evaluation", Blood, vol. 100, no. 11, (2002), Abstract No. 3107.

To the extent the claimed invention is disclosed in the above listed of publication, such disclosure is of mine and Francis J. Giles's invention. The other coauthors listed on the publication, namely Nada Orsolic, Miloslav Beran, Jorge Cortes, Maher Albitar, and Hagop

Kantarjian, are not inventors, and contributed to aspects which were not part of the conception of the subject matter of the claims of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

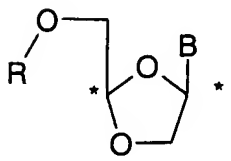
Srdan Verstovsek

Srdan Verstovsek, MD, PhD

Date: 10/14/15

List of Claims:

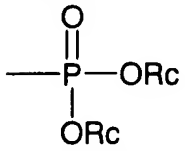
1. A pharmaceutical combination comprising at least one active compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein B is cytosine or 5-fluorocytosine and R is selected from the group comprising H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and



wherein each Rc is independently selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and a hydroxy protecting group;

and a Bcr-Abl tyrosine kinase inhibitor.

2. The pharmaceutical combination according to claim 1, wherein the Bcr-Abl tyrosine kinase inhibitor is imatinib mesylate (STI-571).

3. The pharmaceutical combination according to claim 2, wherein R is H.

4. The pharmaceutical combination according to claim 2, wherein B is cytosine.

5. The pharmaceutical combination according to claim 2, wherein R is H and B is cytosine.

6. The pharmaceutical combination according to claim 2, wherein B is 5-fluorocytosine.

7. The pharmaceutical combination according to claim 2, wherein the compound of formula I is (-)-β-L-Dioxolane-Cytidine (β-L-OddC).

8. The pharmaceutical combination according to Claim 2, wherein the compound of formula I is (-)-β-Dioxolane-5-fluoro-Cytidine (5-FddC).

9. The pharmaceutical combination according to claim 2, wherein the compound of formula I is substantially in the form of the (-) enantiomer.

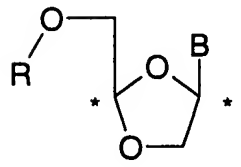
10. The pharmaceutical combination according to claim 2, wherein said compound of formula (I) is at least 97% free of the corresponding (+) enantiomer.

11. The pharmaceutical combination according to claim 2 wherein the compound of formula (I) is β-L-OddC and the Bcr-Abl tyrosine kinase inhibitor is imatinib mesylate (STI-571).

12. A pharmaceutical combination according to claim 2 wherein the compound of formula (I) and imatinib mesylate (STI-571) are present in a ratio between about 1:50 to about 50:1.

13. A pharmaceutical combination according to claim 2 wherein the compound of formula (I) and imatinib mesylate (STI-571) are present in a ratio between about 1:20 to about 20:1.

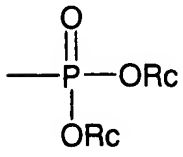
14. A pharmaceutical combination comprising at least one active compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

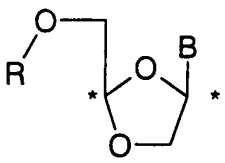
wherein B is cytosine or 5-fluorocytosine and R is selected from the group comprising H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and



wherein each Rc is independently selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and a hydroxy protecting group;

and a Bcr-Abl tyrosine kinase inhibitor and the compound of formula (I) and the Bcr-Abl tyrosine kinase inhibitor are present in a synergistic ratio.

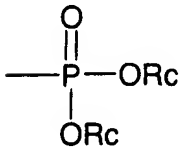
15. A method of treating a patient having leukemia comprising administering to said patient a therapeutically effective amount of a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein B is cytosine or 5-fluorocytosine and R is selected from the group comprising H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and



wherein each Rc is independently selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and a hydroxy protecting group;

and Bcr-Abl tyrosine kinase inhibitor.

16. A method of treating a patient having leukemia according to claim 15 and wherein the ratio of the compound of formula (I) and the Bcr-Abl tyrosine kinase inhibitor is 1:250 to 250:1.

17. The method according to claim 15, wherein the step of administering comprises administering to a patient with acute myelogenous leukemia and chronic myelogenous leukemia.

18. The method according to claim 15, wherein the step of administering comprises administering to a patient with chronic myelogenous leukemia in blastic phase.

19. The method according to claim 15, wherein the step of administering comprises administering to a patient with refractory / relapsed leukemia.

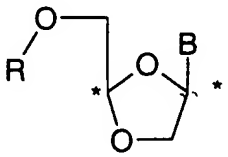
20. The method according to claim 15, wherein the step of administering comprises administering to a patient with refractory / relapsed leukemia and which has been previously treated with imatinib mesylate (STI-571).

21. The method according to claim 15, wherein the step of administering comprises administering to a patient with refractory / relapsed leukemia and which has been previously treated with imatinib mesylate (STI-571) and is resistant to imatinib mesylate (STI-571).

22. The method according to claim 15, wherein the step of administering comprises administering to a patient with refractory / relapsed leukemia and which has been previously treated with imatinib mesylate (STI-571) wherein the compound of formula (I) is β-L-OddC and the Bcr-Abl tyrosine kinase inhibitor is imatinib mesylate (STI-571).

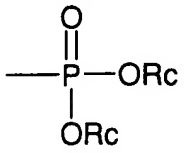
23. The method according to claim 15, wherein the step of administering comprises administering to a patient with refractory / relapsed leukemia and which has been previously treated with imatinib mesylate (STI-571) and wherein the compound of formula (I) is β-L-OddC and the Bcr-Abl tyrosine kinase inhibitor is imatinib mesylate (STI-571) and said combination is a synergistic combination.

24. A method of treating a patient having cancer, other than leukemia, comprising administering to said patient a therapeutically effective amount of a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,
wherein B is cytosine or 5-fluorocytosine and R is selected from the group comprising H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and



wherein each Rc is independently selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and a hydroxy protecting group;

and a Bcr-Abl tyrosine kinase inhibitor;

and at least one further therapeutic agent chosen from a nucleoside analogue and/or a chemotherapeutic agent.

25. A pharmaceutical composition comprising a pharmaceutical combination according to claim 1 and at least one pharmaceutically acceptable carrier or excipient.